Title page: Resistant Hypertension in CKD

2025 Update on Resistant Hypertension in CKD: Where Do We Stand and Where Do We Go?

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Running head: resistant hypertension

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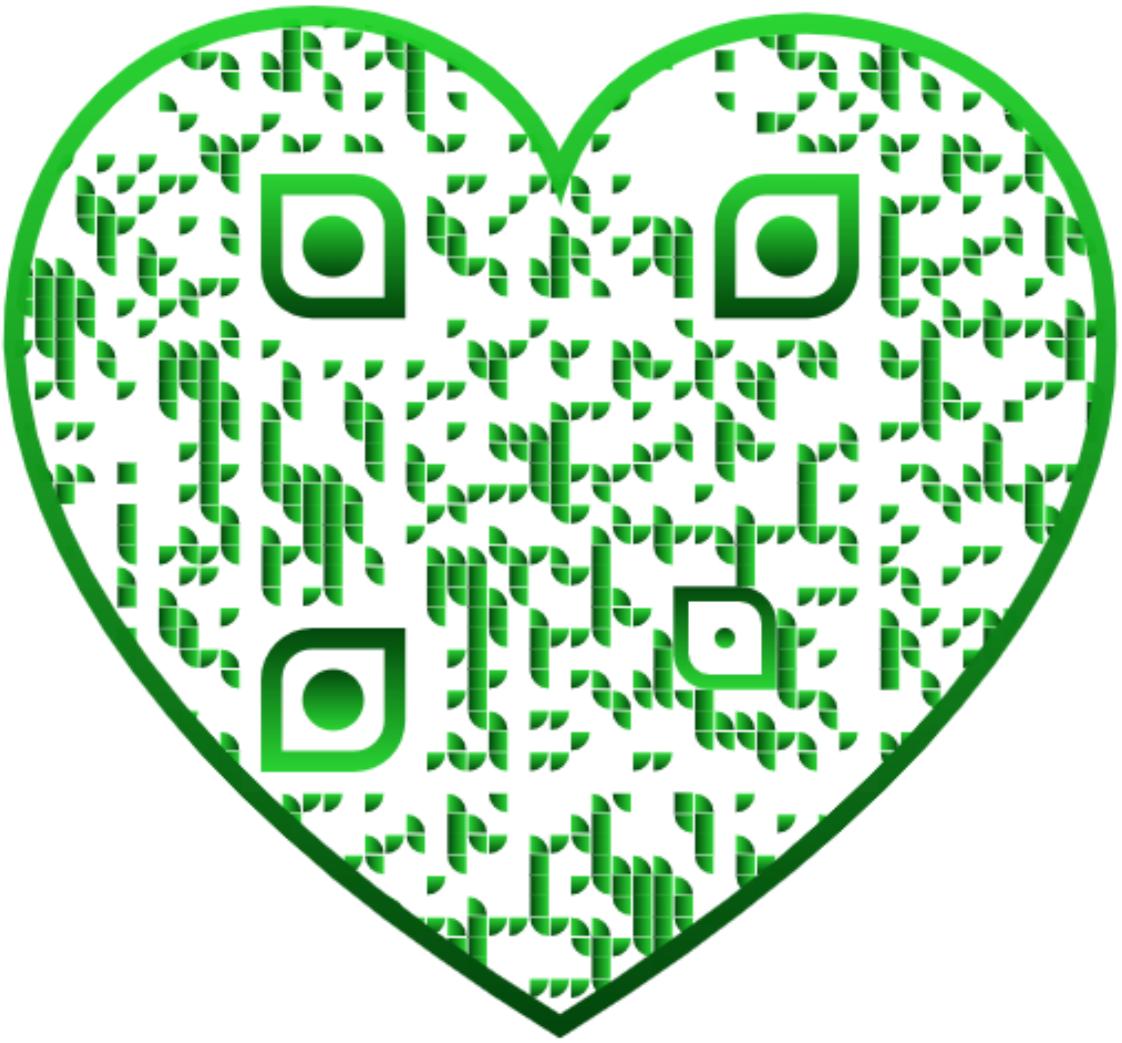

Abstract

Resistant hypertension is highly prevalent among individuals with chronic kidney disease (CKD) and is closely associated with accelerated decline of renal function and increased cardiovascular morbidity and mortality.

Recent clinical guidelines have established clearer blood pressure (BP) targets for this population, generally recommending office BP values below 140/90 mmHg, with a more stringent target of <130/80 mmHg for patients with albuminuria, diabetes, high cardiovascular risk or transplant. Conversely, systolic pressure below 120 mmHg is not advised due to concerns regarding renal hypoperfusion and associated adverse cardiovascular outcomes.

Initial treatment involves an optimised triple therapy regimen with a renin–angiotensin system blocker, a calcium channel blocker, and a diuretic, with the addition of beta-blockers in patients with cardiac comorbidities. Patients with poorly controlled BP require a fourth agent. Spironolactone remains a preferred option when the estimated glomerular filtration rate is ≥30 mL/min/1.73m², but long-term adherence is poor. Chlorthalidone is suitable in more advanced CKD, particularly combined with loop diuretics. Centrally sympatholytic agents represent a valuable alternative.

Sodium-glucose cotransporter 2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and glucagon-like peptide 1 receptor agonists have demonstrated both antihypertensive effects and clear renal and cardiovascular benefits. Dual endothelin receptor antagonist may offer an additional option in patients with resistant hypertension. Renal denervation represents another promising approach. In selected cases of atherosclerotic renovascular disease with high-grade stenosis and clinical risk features, revascularisation may provide benefit.

Collectively, these developments support a more individualised and evidence-based approach to managing resistant hypertension in CKD.

Keywords: aprocitentan, blood pressure targets, chlorthalidone, chronic kidney disease, finerenone, hypertension, renal denervation, SGLT2 inhibitors, spironolactone

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Introduction

Hypertension and chronic kidney disease (CKD) are major risk factors for cardiovascular disease and mortality. These two conditions exhibit a bidirectional relationship: hypertension is a strong predictor of adverse renal outcomes, whereas renal function decline aggravates hypertension. Therefore, achieving an optimal blood pressure (BP) target is vital for the preservation of renal function and improving cardiovascular outcome **(Figure 1)** [1]**.** Nevertheless, resistant hypertension—defined as BP that remains above target despite the use of three optimally dosed antihypertensive agents, including a diuretic—is particularly common among patients with CKD. It affects more than half of individuals with moderate to advanced CKD as well as a substantial proportion of kidney transplant recipients. Persistent hypertension in this cohort is closely associated with higher rates of cardiovascular events and a more rapid loss of kidney function.

Recent guidelines have revised recommendations for BP management in CKD patients and have more clearly defined treatment strategies for resistant hypertension in this subpopulation [2, 3]**.** Established fourth-line agents such as spironolactone and chlorthalidone continue to play a central role, with recent evidence supporting their use even in patients with substantially impaired kidney function. Additional therapeutic options, including sodium-glucose cotransporter 2 (SGLT2) inhibitors, like dapaglifocin and empaglifocin, and non-steroidal mineralocorticoid receptor antagonists (nsMRAs), like finerenone, and glucagon-like peptide 1 receptor agonist (GLP1-RA), like semaglutide, offer both antihypertensive and cardio-renal benefits. Furthermore, endothelin receptor antagonists, such as aprocitentan, and interventional techniques, like renal denervation, are emerging as adjunctive options for selected patients who still demonstrate BP levels beyond the target, or limited tolerance to standard therapies.

As of 2025, the management of resistant hypertension in CKD reflects a more structured and individualized approach, informed by current guidelines and clinical trial data. This review summarizes recent developments and therapeutic strategies to support effective and evidence-based care for this high-risk population. Atherosclerotic renovascular disease (ARVD) is a significant yet frequently overlooked contributor to resistant hypertension and progressive chronic kidney disease (CKD). The joint position statement from the European Renal Best Practice (ERBP) board and the ESH Working Group on Hypertension and the Kidney discusses the diagnostic and therapeutic approaches in detail [4].

Blood Pressure Targets and Measurement in CKD Patients

In 2021, the KDIGO Guideline for the Management of Blood Pressure in CKD advocated for a target systolic BP of <120 mmHg when tolerated, using standardized office measurements [5]. This recommendation was largely based on findings from the SPRINT trial, which demonstrated cardiovascular benefits with intensive BP control (target <120 mmHg) compared to standard control (target <140 mmHg). However, the methodology employed in SPRINT—particularly the use of unattended automated office BP measurement—differs significantly from conventional clinical practice [6, 7]. In a substudy of SPRINT involving ambulatory BP monitoring, average daytime systolic blood pressure (SBP) was 126.5 ± 12 mmHg and 24-hour SBP was 125.4 ± 12 mmHg, while the unattended office SBP was 119.6 ±

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13 mmHg, thus notably lower and not higher, which is usually the case [8, 9]. Such discrepancies raise concerns regarding the real-world applicability of the trial's results. Post-trial surveys conducted across SPRINT centres revealed considerable variability in measurement protocols, suggesting that the trial's reported office BP readings may not be reliably replicated in practice. Comparative analyses suggest that the effective difference in BP may better reflect conventional targets closer to 145 mmHg versus 130 mmHg, rather than the previously assumed 140 versus 120 mmHg [6]. Such findings underscore the critical necessity for standardized measurement techniques when applying guideline targets to clinical practice.

More recently, the 2023 European Society of Hypertension (ESH) Guidelines recommended an office BP target below 140/90 mmHg for the general population. For the majority of patients presenting with CKD, particularly those with albuminuria ≥300 mg/g, diabetes, or elevated cardiovascular risk, a lower threshold of less than 130/80 mmHg is advised (**Figure 2**). These targets also apply to kidney transplant recipients. A SBP below 120 mmHg is not recommended for CKD patients, given the associated risk of reduced renal perfusion and potential adverse cardiovascular events associated with excessive BP lowering [3, 10].

In terms of renal outcomes, the evidence for intensive BP control remains inconclusive. A comprehensive patient-level meta-analysis of seven major trials involving individuals with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² did not reveal a significant overall advantage of intensive BP reduction in terms of kidney-related endpoints. Nonetheless, a subgroup analysis indicated that patients with stage 4–5 CKD (excluding those on dialysis) may experience the benefit of a 20% reduction in the risk of renal progression compared to standard BP targets [11]**.** These subgroup findings reached a borderline significant interaction, implying that the severity of kidney disease could modulate the renal response to BP control. However, given that approximately 40% of patients included in this meta-analysis originated from the SPRINT trial concerns persist related to methodological consistency.

Pharmacologic Therapy in Resistant Hypertension and CKD

According to current guidelines, the three main pillars of hypertension treatment in CKD patients are an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and a thiazide or thiazide-like diuretic [3]. This initial combination of drugs is recommended in all populations, regardless of whether the eGFR is above or below 30 mL/min/1.73m². However, since the effectiveness of thiazides diminishes as kidney function declines, in patients with eGFR below 30 mL/min/1.73m² they are typically replaced by loop diuretics. In routine clinical practice, however, this transition often occurs even earlier, at eGFR around 40 mL/min/1.73m², to ensure adequate diuretic response [3].

True resistant hypertension is characterized by persistently elevated BP despite the judicious use of optimized triple therapy, including a diuretic. This condition reportedly affects more than half of CKD patients and up to 75% of kidney transplant recipients. According to the 2023 ESH Guidelines, the treatment algorithm for resistant hypertension in the CKD population is contingent upon the eGFR level (**Figure 3**). For individuals with an eGFR ≥30 mL/min/1.73m²,

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there are several options, including beta-blockers, alpha-blockers and centrally acting agents, with spironolactone (or other nsMRAs) as the preferred fourth-line agent. Conversely, for those with eGFR <30 mL/min/1.73m², chlorthalidone is recommended as the preferred initial addition, despite a known caution against thiazide-like diuretics in advanced CKD [3]. This recommendation is based on the pharmacological properties of chlorthalidone, such as a longer half-life and more sustained BP-lowering profile compared to hydrochlorothiazide (HCTZ). While some studies show no difference in cardiovascular outcomes between these two groups when doses are matched (e.g. 25–50 mg HCTZ ≈ 12.5–25 mg chlorthalidone), chlorthalidone may offer advantages in patients with volume overload and reduced nephron mass [12]. Namely, the CLICK trial investigated the effects of chlorthalidone in patients with advanced CKD (eGFR 15–30 mL/min/1.73 m²) and poorly controlled hypertension who were already on loop diuretics and renin-angiotensin-aldosterone system (RAAS) blockers. After 12 weeks, 24-hour ambulatory systolic BP was reduced by 10.5 mmHg (–11.0 mmHg vs –0.5 mmHg; p<0.001). However, 45% of patients in the chlorthalidone arm exhibited a ≥25% increase in serum creatinine. Additional adverse effects included hypokalemia (10%), hyponatremia (11%), hyperuricemia (20%), and dizziness (25%) [13].

A notable insight derived from a prespecified subgroup analysis of the CLICK trial indicates that chlorthalidone led to a greater reduction in SBP among the participants concurrently administered loop diuretics compared to those not receiving this class of diuretics. This finding suggests a potential synergistic effect stemming from the combined use of these medications. Such observations support the strategy of sequential nephron blockade which aims to optimize diuretic effectiveness by targeting sodium reabsorption at different tubular segments. The physiologic rationale is well established: loop diuretics act on the thick ascending limb of the loop of Henle, while thiazide-like agents, including chlorthalidone, target the distal convoluted tubule. Their concurrent administration facilitates a more comprehensive reduction in sodium reabsorption and improves BP control in patients with sodium-retentive states such as advanced CKD.

Spironolactone is considered to be one of the most effective pharmacologic interventions for the management of resistant hypertension. In the PATHWAY-2 trial it significantly lowered home SBP compared to placebo, bisoprolol, and doxazosin in patients already receiving triple therapy, clearly establishing its role as an effective fourth-line agent [14]. Based on these findings, the 2024 European Society of Cardiology Guidelines endorsed spironolactone as the preferred addition to the treatment in resistant hypertension [1]. However, important limitations must be acknowledged regarding the applicability of these findings. Notably, patients with an eGFR below 45 mL/min/1.73m² were excluded from the PATHWAY-2 trial, thereby restricting the generalizability of the results to a significant portion of the CKD population. Furthermore, follow-up was confined to three months, limiting the insight into long-term safety and tolerability. Real-world data indicates that, even under routine care, fewer than 50% of patients remain adherent to spironolactone after one year of treatment, largely due to issues such as hyperkalemia, worsening renal function and progesterone-related side effects (e.g. gynecomastia, sexual dysfunction). The potassium values recorded in PATHWAY-2 reflect only short-term exposure and may underestimate the real risk accumulating over time. Also, the superior antihypertensive efficacy of spironolactone in PATHWAY-2 was observed with a 50 mg dose. When used at 25 mg, which is more common

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in the context of CKD, the resultant reduction in blood pressure did not surpass that achieved with doxazosin or bisoprolol [14]. Despite the outlined limitations that restrict spironolactone applicability to patients with CKD, there remains a notable absence of outcome trials within general hypertensive populations without concomitant heart failure. Therefore, additional evidence is warranted to confirm cardiovascular risk reduction outside of that context. In clinical practice, spironolactone may be an option, but should not be regarded as the default choice, particularly in patients with an eGFR below 45 mL/min/1.73m^2.

Central sympatholytic agents, such as clonidine, may serve as a practical alternative when MRAs are contraindicated or poorly tolerated. The results from the ReHOT trial indicate that clonidine and spironolactone achieve comparable rates of BP control —approximately 25–28%—after three months of treatment in patients with resistant hypertension already receiving triple therapy [15]. Both agents facilitated gradual and sustained BP reductions, with no significant difference in efficacy. Although clonidine's use is tempered by side effects such as sedation and dry mouth, explaining its preferential evening administration, and there exists a risk of rebound hypertension if withdrawn abruptly, it remains a viable option in select patients, particularly those with hyperkalemia or advanced CKD.

Aprocitentan, a dual endothelin receptor antagonist, has emerged as a promising new agent in the treatment of resistant hypertension, particularly for individuals in whom conventional therapies are limited by renal dysfunction or electrolyte disturbances. The efficacy of aprocitentan was evaluated in the Phase 3 PRECISION trial, a robust, randomized, multicentre study, which demonstrated significant and sustained BP reduction among patients with confirmed resistant hypertension [16]. The methodology involved a three-phase design: an initial 4-week double-blind comparison with placebo, followed by 32-week single-blind treatment phase, and a final 4-week double-blind withdrawal. In the initial phase, both 12.5 mg and 25 mg doses significantly lowered unattended office systolic and diastolic BP compared to placebo, with effects sustained throughout the treatment period and reversed upon drug withdrawal, thus confirming the durability of its antihypertensive action. Recent subgroup analyses presented at the American Society of Nephrology Kidney Week 2024 provided further insights into aprocitentan's usage in patients with CKD. In those classified as high or very high risk according to KDIGO criteria, both daytime and nighttime ambulatory SBP decreased substantially—up to –9.6 mmHg at the 12.5 mg dose. However, fluid retention emerged as a frequent adverse event, reported in 15.7% of subjects during the initial treatment phase and escalating to 31.7% with prolonged use. Although most cases were manageable through diuretic adjustments, a small number of patients ultimately discontinued treatment.

As for the practical implications of the trial findings, it is generally advocated to start with the lower dose of aprocitentan. This recommendation stems from the observation that there was no substantial difference in BP reduction between the 12.5 and 25 mg doses. Concerns about potential fluid retention may require the addition of diuretics or discontinuation of the medication in certain patients. Aprocitentan may offer a valuable therapeutic option for select patient populations, and further clinical experience will help clarify its role in practice. Nevertheless, one notable limitation to broader use is its high cost, which may hinder accessibility within routine clinical practice.

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The Role of Novel Nephroprotective Agents in Hypertensive CKD patients

The 2023 ESH Guidelines emphasize a stepwise, combination-based approach for managing hypertension in CKD, incorporating both traditional antihypertensive agents and newer, nephroprotective therapies [3]. SGLT2 inhibitors and finerenone are particularly emphasized, alongside lifestyle modifications and antihypertensive drug therapy. Use of an SGLT2i is recommended in CKD patients with a moderate to severe increase in albuminuria and an eGFR of at least 20 mL/min/1.73m^2 regardless of the presence of diabetes, while finerenone is advised in patients with CKD associated with type 2 diabetes and moderate or severe albuminuria, provided that eGFR is at least 25 mL/min/1.73m^2 and serum potassium is <5.0 mmol/L.

Strong evidence from a large meta-analysis of renal and cardiovascular outcome trials in both diabetic and non-diabetic patients supports this recommendation. The analysis included DAPA-CKD and EMPA-KIDNEY trials, both showing roughly a 40% relative risk reduction in hard kidney outcomes—such as sustained eGFR decline, kidney failure, and renal death—regardless of diabetes status. Often forgotten to emphasize, both therapies effectively lower BP in hypertensive patients, and their consistently strong renal effects, especially in trials with kidney outcomes as the primary endpoint, strongly support their place in the updated antihypertensive treatment strategies [17]. Additionally, SGLT2 inhibitors also appear to lower the risk of hyperkalemia when combined with other therapies, such as RAAS blockers or finerenone. Across multiple trials, this combination was associated with a 16–18% overall reduction in hyperkalemia risk, with some high-risk groups seeing reductions of up to 80%. Given how often elevated potassium limits the use of essential medications in CKD, this added benefit further supports the role of SGLT2 inhibitors in managing resistant hypertension in these patients [18].

A key clinical question concerns the efficacy and safety of SGLT2i in patients with more advanced kidney disease, particularly stage 4 CKD. Although most large trials excluded participants with an eGFR below 25 mL/min/1.73m², subgroup analyses from the DAPA-CKD trial provide reassuring evidence. Patients in stage 4 CKD experienced a clear benefit from dapagliflozin in terms of hard renal outcomes, without an increase in serious adverse events compared to placebo [19]. Importantly, the treatment was not stopped based on eGFR decline alone—discontinuation occurred only in cases of pregnancy, diabetic ketoacidosis, or other significant adverse events. Even when eGFR dropped below 15 mL/min/1.73m², patients often remained on treatment. The initial decline in eGFR observed with dapagliflozin was also less pronounced in stage 4 CKD compared to earlier stages, indicating a more stable hemodynamic response. These findings support the concept that SGLT2 inhibitors can be safely continued in patients with advanced CKD and that discontinuing therapy solely based on an eGFR threshold may not be necessary and potentially increases cardiovascular events.

Finerenone, a non-steroidal mineralocorticoid receptor antagonist, has emerged as another promising option in the treatment of patients with CKD and type 2 diabetes, even though its antihypertensive effect has often been underestimated. In the FIDELIO-DKD trial only a 2 to 3 mmHg difference was observed between finerenone and placebo, despite efforts to level BP through adjustments of concomitant antihypertensive medications. In contrast, the ARTS-DN

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phase 2b trial involving 823 patients with type 2 diabetes and CKD reported placebo-adjusted changes in 24-hour ambulatory BP monitoring of -8.3 mmHg for finerenone 10 mg, -11.2 mmHg for 15 mg, and -9.9 mmHg for 20 mg (n = 31) after three months [20].The FIDELITY pooled analysis, combining data from FIDELIO-DKD and FIGARO-DKD trials, demonstrated a 23% relative risk reduction in kidney disease progression and a 14% reduction in cardiovascular morbidity and mortality compared to placebo [21]. These benefits were further explored in a pre-specified subgroup analysis focused on patients with stage 4 CKD [22]. In this higher-risk population, the cardiovascular benefit of finerenone became evident within the first year of treatment, while the renal endpoint—defined as time to kidney failure, sustained ≥57% eGFR decline, or renal death—showed a clear separation from placebo over the first two years of follow-up. While the protective effects may diminish over time as patients progress toward end-stage renal disease, the evidence supports the use of finerenone in advanced CKD, expanding its therapeutic applicability. Thus, finerenone lowers blood pressure significantly, but no comparative study to spironolactone has been conducted. Ongoing studies will define the nephroprotective properties in CKD patients without type 2 diabetes.

Recent data on the cardiovascular and nephroprotective effects of GLP-1RAs have emerged following the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines. The FLOW trial, which designated a renal endpoint as its primary objective, demonstrated that semaglutide significantly reduced the risk of primary outcome events by 24%, kidney-specific outcomes by 21%, and cardiovascular mortality by 29% in patients with type 2 diabetes and CKD [23]. Moreover, several GLP-1RAs have been shown to exert considerable antihypertensive effects, primarily related to their pronounced weight reduction capabilities. Although their antihypertensive effects only partially explain their nephroprotective and cardioprotective benefits, GLP-1RAs have become valuable adjunctive antihypertensive agents for patients with CKD.

Aldosterone synthase inhibitors have emerged as new pharmacological tools that expand our treatment options for resistant hypertension and the harmful effects of aldosterone on the cardiovascular and renal systems. Patients with aldosterone dysregulation are at an increased risk of chronic kidney disease (CKD) progression towards end-stage renal disease (ESRD). Thus, blocking aldosterone synthesis not only reduces blood pressure, but may also exert nephroprotective effects beyond blood pressure control. Indeed, the most recently published data revealed a significant decrease in blood pressure in patients with resistant hypertension following treatment with baxdrostat. Furthermore, treatment with vicadrostat was found to reduce albuminuria in a dose-dependent manner in conjunction with renin–angiotensin system inhibition and empagliflozin in patients with CKD [24, 25].

Targeting angiotensin synthesis in the liver with RNA interference therapeutic molecules, such as zilebesiran, has been demonstrated to reduce angiotensinogen concentrations and blood pressure in cases of mild to moderate hypertension, and lead to even greater reductions in blood pressure in patients with uncontrolled hypertension [26]. Once approved, this new therapeutic option will offer better adherence to drug therapy, since only one subcutaneous injection is required every six months.

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Renal Denervation in the Treatment of Hypertension in CKD

Renal denervation (RDN) has gained recognition as a potential therapeutic option within the treatment algorithm for true resistant hypertension. Renal sympathetic nerves play crucial roles in regulating renin secretion, sodium absorption and renal vascular resistance, thus influencing systemic BP and fluid volume (**Figure 4**). Recent sham-controlled trials using second-generation RDN technologies have demonstrated significant reductions in both office and 24-hour ambulatory BP after a successful denervation procedure. A meta-analysis of these trials reported a mean sham-corrected decrease of 4.4 mmHg in 24-hour ambulatory systolic BP and 6.6 mmHg in office systolic BP compared to sham procedures, with greater absolute reductions observed in clinical settings (averaging around 10 mmHg in office BP) [3, 27].

In November 2023, the U.S. Food and Drug Administration agency approved both radiofrequency- and ultrasound-based RDN systems in cases of resistant hypertension. European hypertension and cardiology societies now acknowledge RDN as an appropriate option for true resistant hypertension, emphasizing the importance of shared decision-making when conventional therapies fail [3]. Across various studies, the following predictors of preferring RDN were identified: younger age; male sex; higher office or home blood pressure (BP); the need for more antihypertensive medication; cardiovascular comorbidities; side effects; and poor drug adherence [28]. To date, eGFR should be >40 ml/min/1.73 m², according to guideline recommendations; below this arbitrary cut-off, strong evidence of the efficacy and safety of RDN is limited, though steadily increasing. It should be noted that RDN is an option for achieving target blood pressure (instead of adding another drug), but patients with CKD will still need to take multiple medications to maximise nephroprotection.

In CKD, data are more limited, but encouraging. Three pilot studies reported a stabilization of renal function after renal denervation in patients with CKD stage 3 in parallel to a significant decrease in BP [29]. A recent randomized, sham-controlled trial demonstrated that ultrasound-based RDN significantly reduced 24-hour ambulatory diastolic BP (–5.90 mmHg; p=0.035) and daytime ambulatory BP (–6.85 mmHg; p=0.030) at six months in patients with CKD and true resistant hypertension [30]. Despite the small sample size (10 patients per arm), the hemodynamic response was consistent and promising. Nonetheless, these findings reinforce the potential role of RDN in select CKD patients, particularly those with limited pharmacologic options or who express strong preference for a non-pharmacologic option.

Longer-term data from the Global SYMPLICITY Registry offered additional insight. Among 475 CKD patients followed over three years, 24-hour systolic BP reductions were comparable to those seen in non-CKD cohorts, with no significant differences between groups [31]. Notably, antihypertensive efficacy was sustained despite lower baseline eGFR (mean 47 ± 10 mL/min/1.73 m²), suggesting that CKD does not blunt the long-term effect of RDN. Unpublished data of the Global SYMPLICITY Registry with a larger sample size confirm the observation that renal denervation in CKD patients achieves a sustained BP decrease over at least 3 years (in non CKP patients up to 10 years have been reported) and this observation has

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been made for CKD stages 3 and 4. These findings support the use of RDN in appropriately selected patients with CKD.

Conclusion

Resistant hypertension in patients with CKD continues to present a major clinical challenge, contributing to poor cardiovascular outcomes and faster progression of kidney dysfunction. In recent years, clearer guidance and stronger evidence have emerged to help clinicians manage this high-risk group more effectively. Office blood pressure should be maintained below 140/90 mmHg in all CKD patients, with lower targets (<130/80 mmHg) for those with higher cardiovascular or renal risk. However, reductions below 120/70 mmHg are not recommended due to potential harm. Following optimized triple therapy, the addition of a fourth agent is guided by kidney function. Spironolactone remains a preferential add-on in patients with eGFR ≥30 mL/min/1.73m², while chlorthalidone is suitable even when eGFR falls below this threshold, particularly in combination with loop diuretics to enhance natriuresis and overcome diuretic resistance. Central sympatholytic agents represent a valuable option in patients with CKD as well. Although not approved as antihypertensive agents, nephroprotective therapies now form an essential part of antihypertensive treatment, since the antihypertensive properties of SGLT2 inhibitors, nsMRAs and GLP1-RAs support to achieve target BP. SGLT2 inhibitors are indicated for patients with eGFR ≥20 mL/min/1.73m² and albuminuria, offering renal and cardiovascular benefits independent of glycemic control. Finerenone is recommended for patients with CKD and type 2 diabetes who have persistent albuminuria and an eGFR of 25 mL/min/1.73m² or higher, as long as serum potassium levels remain below 5.0 mmol/L. Additionally, GLP1-RAs are advised for patients with type 2 diabetes and CKD. Renal denervation may represent an adjunctive option in CKD patients This algorithmic framework reflects a shift toward targeted, physiology-informed care for resistant hypertension in CKD. Incorporating guideline-directed pharmacologic therapy—including the appropriate fourth-line drug—alongside nephroprotective agents and selective intervention strategies, offers a path to improved outcomes in this high-risk population.

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Data availability statement

No new data were generated or analysed in support of this research.

Acknowledgements

The topic of this Review was also presented during the 62nd Congress of the European Renal Association in Vienna on June 4-7, 2025.

Conflict of interest statement

None declared.

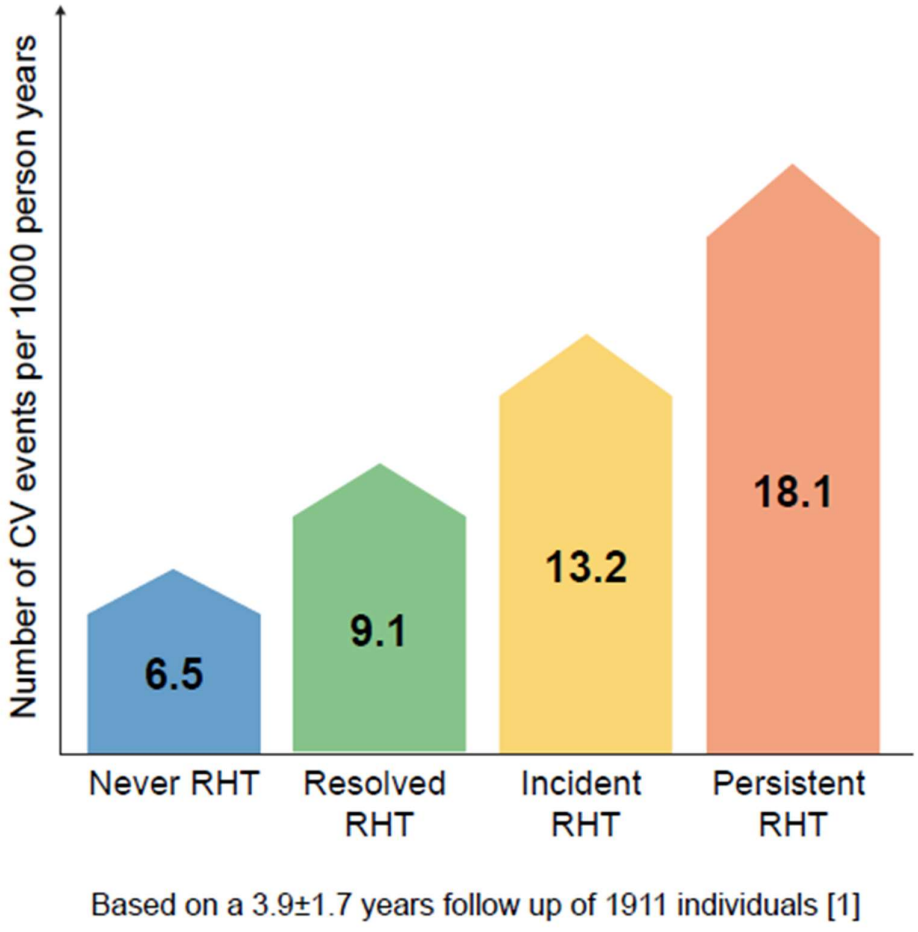

Figure 1. Relationship between resistant hypertension treatment and incidence of cardiovascular events

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< 140/90 mmHg	All CKD patients
< 130/80 mmHg	CKD + albuminuria ≥ 300mg/g, diabetes, cardiovascular risk or transplant
< 120/70 mmHg	Not recommended!

Figure 2. Blood pressure targets for CKD patients according to 2023 ESH Guidelines for the Management of Arterial Hypertension

	Fundamental (preferential SPC)	Fourth step	Alternative	Nephroprotective
All CKD stages	ACEi/ARB + CCB	BB if cardiac comorbidities	+ BB/α1 blocker or centrally acting agent	SGLT2 inhibitors (eGFR > 20 ml/min/1.73 m^2)
CKD 1–3	+ T/T_L diuretic	+ Spironolactone or other MRA	Renal denervation in specific patients	nsMRAs (finerenone) (eGFR > 25 ml/min/1.73 m^2)
CKD 4–5ND	+ Loop diuretic	+ Chlortalidone or other T/T_L diuretic		GLP1-RA (semaglutide)

Figure 3. Summary of current antihypertensive options for the treatment of true resistant hypertension in different stages of CKD
Legend: CKD – chronic kidney disease, ND – non-dialysis, ACEi – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, CCB – calcium channel blocker, T/T_L – thiazide/thiazide-like, MRA – mineralocortiocoid receptor antagonist, BB – beta blocker, SGLT2 – sodium-glucose transporter 2, nsMRA – non-steroidal mineralocorticoid receptor antagonist, GLP1-RA – glucagon-like peptide 1 receptor agonist

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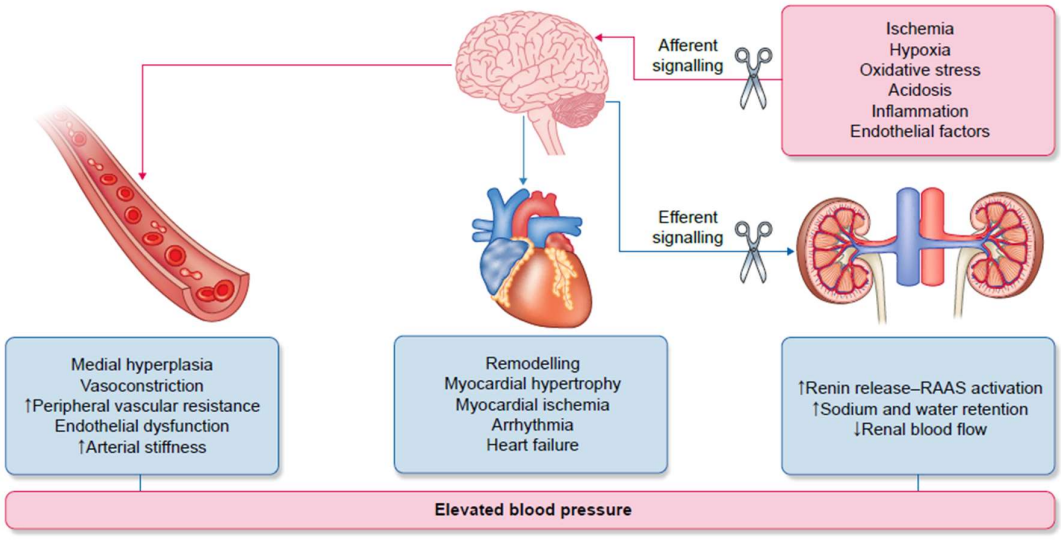

Figure 4. The rationale for renal denervation – Effects of increased sympathetic signalling on peripheral organs and circulation contributing to hypertension

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